Pd-catalysed heteroarylations of 3-bromochromen-4-one via C-H bond activation of heteroarenes.

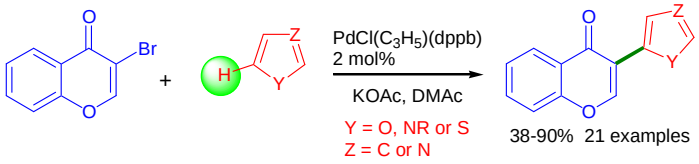
Fatma Belkessam, Fazia Derridj, Liqin Zhao, Abdelhamid Elias, Mohand Aidene, Safia Djebbar, Henri Doucet

Graphical Abstract

Pd-catalysed heteroarylations of

3-bromochromen-4-one via C-H bond activation of heteroarenes

Fatma Belkessam,[a,b] *Fazia Derridj,*[a,c] *Liqin Zhao,*[a] *Abdelhamid Elias,*[b] *Mohand Aidene,*[b] *Saffia Djebbar,*[c] *Henri Doucet,*[a*]



Pd-catalysed heteroarylations of 3-bromochromen-4-one via C-H bond activation of heteroarenes

Fatma Belkessam,[a,b] Fazia Derridj,[a,c] Liqin Zhao,[a] Abdelhamid Elias,[b] Mohand Aidene,[b] Saffia Djebbar,[c] Henri Doucet,[a*]

[a]*Institut Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes "Catalyse et Organometalliques", Campus de Beaulieu, 35042 Rennes, France.*
[b]*Département de chimie, Tizi Ouzou University, BP 17 RP 15000 Tizi-Ouzou, Algeria.*
[c] *Laboratoire d'hydrométallurgie et chimie inorganique moléculaire, Faculté de Chimie, U.S.T.H.B. Bab-Ezzouar, Alger, Algeria.*

Abstract

The palladium-catalysed direct coupling of 3-bromochromen-4-one with heteroaromatics was found to proceed in moderate to high yields. A wide variety of heteroaromatics can be coupled with this chomenone derivative using 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst and KOAc as the base. Moreover, the reaction tolerates a range of useful functional groups on the heteroarene.

Several flavones and chromen-4-one derivatives containing an (hetero)aryl substituent, such as Pranlukast, Cromitrile, Puerarin, Hesperetin or Naringinine have been found to a display useful bioactivities; Eriodictyol is a natural product which has taste-modifying properties (Fig 1). Therefore, the discovery of simple procedures for the preparation of a variety of (hetero)arylated chromen-4-ones would provide powerful tools for pharmaceutical researchers.

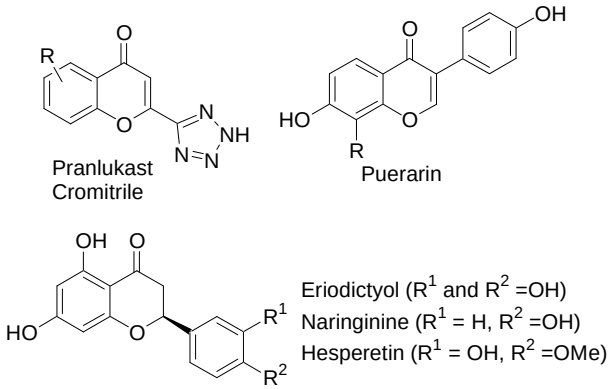
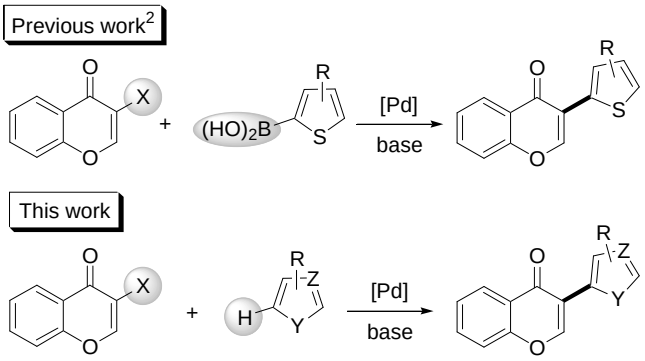


Figure 1 Examples of bioactive chromen-4-one derivatives

A classical method to prepare 3-(hetero)arylated chromen-4-one derivatives is to employ a 3-halochromen-4-one with a (hetero)aryl boronic acid derivative using a palladium catalyst (Scheme 1, top).[1,2] However, these reactions require the preliminary preparation of $HetArB(OR)_2$, which might be tricky in several cases due to the poor stability of some of these heteroarylboronic acids. Moreover, these couplings provide a boron salt as by-product.

In recent years, the palladium-catalysed direct coupling of heteroaromatics with *aryl*-halides or *vinyl*-halides proved to be an extremely powerful method for the synthesis of arylated or vinylated heteroaromatics.[3-6] On the other hand, to our knowledge, palladium-catalysed direct heteroarylations using 3-halochromen-4-ones has not been reported (Scheme 1, bottom).[7] The use of such reactants, which are commercially available, would allow to prepare a wide variety of 3-heteroarylchromen-4-ones in only one step. Moreover, their asymmetric reduction should allow the synthesis of useful chiral chromanones.[8]

∗ Corresponding author. Tel.: 00-33-2-23-23-63-84; fax: 00-33-2-23-23-69-39; e-mail: henri.doucet@univ-rennes1.fr

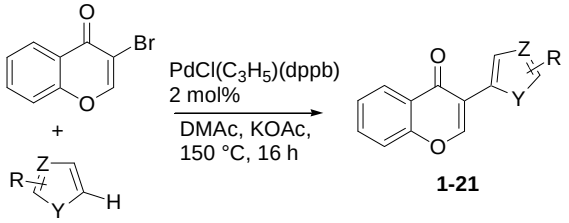


Scheme 1

Here, we wish to report (i) on influence of the conditions for palladium-catalysed direct coupling of 3-bromochromen-4-one with 2-*i*butylthiazole, and (ii) show the scope of this coupling using a set of heteroaromatics.

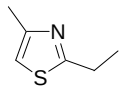
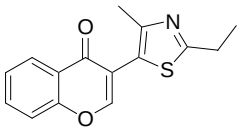
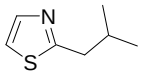
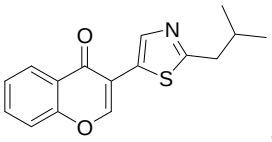
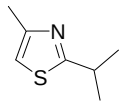
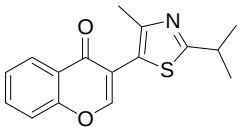
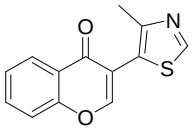
First, we examined the reactivity of 3-bromochromen-4-one for the palladium-catalysed direct coupling with 2-ethyl-4-methylthiazole using 2 mol% $PdCl(C_3H_5)(dppb)$ as the catalyst, DMAc as the solvent and KOAc as the base (Scheme 2, table 1, entry 1). These conditions had been previously found operative for similar reactions.[5a] Using these conditions, a complete conversion of this bromide derivative was observed, and the desired coupling product **1** was isolated in 83% yield (Table 1, entry 1). In the presence of only 0.5 mol% $PdCl(C_3H_5)(dppb)$ a conversion of 96% of 3-bromochromen-4-one was observed to give **1** in 78%; whereas, a lower conversion of 90% was obtained with 2 mol% of ligand-free $Pd(OAc)_2$ catalyst (Table 1, entries 2 and 3). A moderate yield in **1** was formed for the reaction performed in greener solvent diethyl carbonate (Table 1, entry 4).

Then, we extended the scope of the heteroarylation of 3-bromochromen-4-one to a variety of thiazole derivatives (Table 1). From 2-*i*butylthiazole or 4-methyl-2-*i*propylthiazole, the desired products **2** and **3** were also obtained in very good yields of 89% and 88% (Table 1, entries 5 and 6). We also examined the reactivity of 4-methylthiazole.



Scheme 2

Table 1. Palladium-catalysed direct coupling of thiazoles with 3-bromochromen-4-one (Scheme 2).[11]

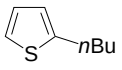
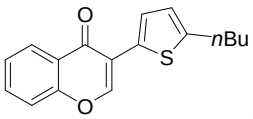
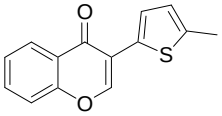
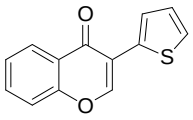
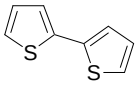
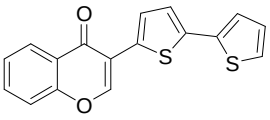
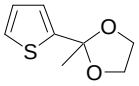
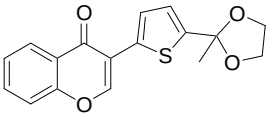
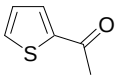
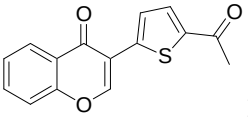
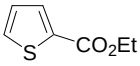
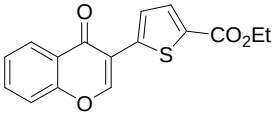
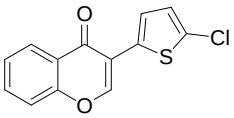
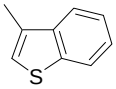
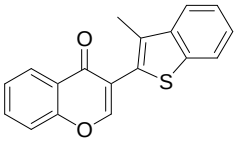
Entry	Heteroarene	Product	Yield (%)
1		 **1**	83
2			78[a]
3			72[b]
4			43[c]
5		 **2**	89
6		 **3**	88
7		 **4**	81

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), 3-bromochromen-4-one (1 mmol), thiazole derivative (2 mmol), KOAc (2 mmol), DMAc, 16 h, 150 °C, isolated yields. [a] $PdCl(C_3H_5)(dppb)$ (0.005 mmol). [b] $Pd(OAc)_2$ (0.02 mmol). [c] diethylcarbonate as the solvent.

With this thiazole derivative, we might have observed the formation of both the C2 and C5 arylated thiazoles, as in the presence of Cs_2CO_3, a selective arylation at C2, which proceed via a non-concerted metalation-deprotonation, followed by an arylation at C5, has been reported.[9,10] However, in the presence of KOAc as the base/ligand, a high yield of **4**, due to a completely regioselective arylation at C5, was obtained (Table 1, entry 7). This high regioselectivity can be explained by the nature of the base (KOAc) which favours a concerted-metallation-deprotonation mechanism (CMD).[9]

We then examined the reactivity of several thiophene derivatives for the coupling with 3-bromochromen-4-one (Table 2). From 2-*n*-butylthiophene, **5** was obtained in 72% yield due to a partial conversion the 3-bromochromen-4-one (Table 2, entry 1). As expected a similar yield was obtained using 2-methylthiophene (Table 2, entry 2). The reaction of unsubstituted thiophene also proceeds to give the desired coupling product **7** in 69% yield (Table 2, entry 3).

Table 2. Palladium-catalysed direct coupling of thiophenes with 3-bromochromen-4-one (Scheme 2).[11]

Entry	Heteroarene	Product	Yield (%)
1		 **5**	72
2		 **6**	75
3		 **7**	69[a]
4		 **8**	67
5		 **9**	70
6		 **10**	59
7		 **11**	38
8		 **12**	68
9		 **13**	67

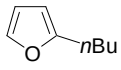
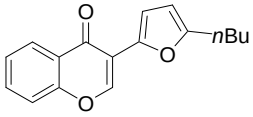
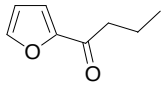
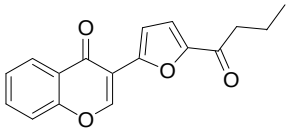
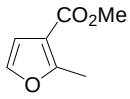
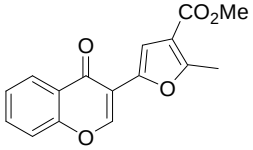
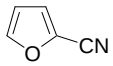
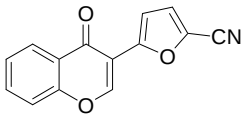
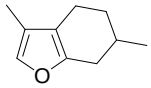
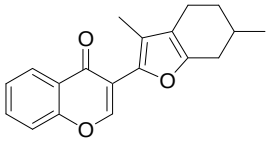
Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), 3-bromochromen-4-one (1 mmol), thiophene derivative (2 mmol), KOAc (2 mmol), DMAc, 16 h, 150 °C, isolated yields. [a] thiophene: 4 mmol.

For this reaction, 4 equiv. of thiophene were employed in order to avoid the formation of 2,5-disubstituted thiophene. With [2,2']bithiophenyl, the desired product **8** was also obtained in good yield (Table 2, entry 4). We also examined the reactivity of thiophenes bearing functional groups. From protected or non-protected 2-acetylthiophenes, **9** and **10** were obtained in 70% and 59% yields, respectively (Table 2, entries 5 and 6). A moderate yield in **11** was obtained with ethyl thiophene-2-carboxylate due to an important formation of unidentified side-products (Table 2, entry 7). This might be due to partial decarboxylation of this thiophene derivative. On the other hand, from 2-chlorothiophene, the desired product **12** was produced in high yield (Table 2, entry 8). It should be noted that no cleavage of the C-Cl bond of this thiophene derivative was observed allowing further transformations. Finally, 3-methylbenzothiophene was successfully employed to give the C2-substituted benzothiophene **13** in 67% yield (Table 2, entry 9).

Several furan derivatives were also employed successfully to provide 3-furanylchromene-4-ones (Table 3). For example, in the presence of 2-*n*-butylfuran, **14** was produced in 60% yield (Table 3, entry 1). 2-Butyrylfuran and methyl 2-methylfuran-3-carboxylate also reacted quite nicely the give **15** and **16** in 56% and 67% yields, respectively (Table 3, entries 2 and 3). A moderate yield of 46% in **17** was obtained from furan-2-carbonitrile due to some formation of the homo-coupling product of 3-bromochromen-4-one (Table

3, entry 4). Finally, we examined the reactivity of menthofuran. This 2,3,4-trisubstituted furan, which is naturally present in mint oil, was also found to be reactive for the direct coupling with 3-bromochromen-4-one (Table 3, entry 5). The desired product **18** was obtained in 78% yield.

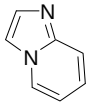
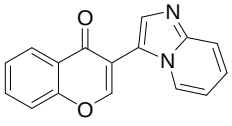
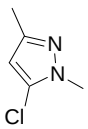
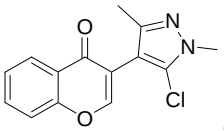
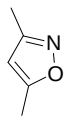
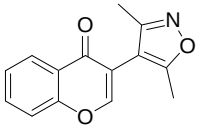
Table 3. Palladium-catalysed direct coupling of furans with 3-bromochromen-4-one (Scheme 2).[11]

Entry	Heteroarene	Product	Yield (%)
1		 **14**	60
2		 **15**	56
3		 **16**	67
4		 **17**	46
5		 **18**	78

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), 3-bromochromen-4-one (1 mmol), furan derivative (2 mmol), KOAc (2 mmol), DMAc, 16 h, 150 °C, isolated yields.

Finally, the reactivity of imidazo[1,2-a]pyridine, 5-chloro-1,3-dimethylpyrazole and 3,5-dimethylisoxazole was examined (Table 4). Activation of C-H bond at C3 of imidazo[1,2-a]pyridine provides **19** in 90% yield. Lower yields of 57% and 66% in **20** and **21** were obtained for the coupling at C4 of 5-chloro-1,3-dimethylpyrazole or 3,5-dimethylisoxazole due to partial conversions of the 3-bromochromeneone.

Table 4. Palladium-catalysed direct coupling of various heteroarenes with 3-bromochromen-4-one (Scheme 2).[11]

Entry	Heteroarene	Product	Yield (%)
1		 **19**	90
2		 **20**	57
3		 **21**	66

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), 3-bromochromen-4-one (1 mmol), heteroarene (2 mmol), KOAc (2 mmol), DMAc, 16 h, 150 °C, isolated yields.

In summary, we have demonstrated that 3-bromochromen-4-one can be heteroarylated with a variety of heteroarenes via palladium-catalysed C-H bond activation using an air-stable palladium catalyst. Functional groups such as chloro, acetyl, nitrile or ester on the heteroarene are tolerated. This procedure is economically attractive as both 3-bromochromen-4-one and a wide variety of hereroarenes are commercially available and as this procedure employ a moderate loading of palladium catalyst and an inexpensive base. Another advantage is the reduction of number of steps to prepare these heteroarylated chromenones compared to Suzuki coupling reactions.

Acknowledgments

We thank the Centre National de la Recherche Scientifique and "Rennes Metropole" for providing financial support. The authors are grateful to the "Région Bretagne" for a PhD grant to Kassem Beydoun.

References and notes

1. For examples of palladium cross-couplings with heteroaromatic compounds: a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*, Pergamon, Amsterdam, 2000; b) Ackermann, L. *Modern arylation methods*, Wiley-VCH, Weinheim, 2009.
2. For the synthesis of 3-heteroarylated chromen-4-ones uzing Suzuki coupling: a) Yokoe, I.; Sugita, Y.; Shirataki, Y. *Chem. Pharm. Bull.* **1989**, *37*, 529-530; b) Zhu, Q.; Wu, J.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 3333-3336; c) Joo, Y. H.; Kim, J. K.; Kang, S.-H.; Noh, M.-S.; Ha, J.-Y.; Choi, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413-417; d) Ding, K.; Wang, S. *Tetrahedron Lett.* **2005**, *46*, 3707-3709; e) Peng, W.-J.; Han, X.-W.; Yu, B. *Chin. J. Chem.* **2006**, *24*, 1154-1162.
3. a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238; b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200-205; c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35-41; d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173-1193; e) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949-957; f) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269-10310; g) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; h) Chen, X.; Engle, K. M.; Wang D.-H.; Yu J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115; i) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20-40; j) Fischmeister, C.; Doucet, H. *Green Chem.* **2011**, *13*, 741-753; k) Mori, A. *J. Syn. Org. Chem. Jpn.* **2011**, *69*, 1202-1211; l) Kuhl N.; Hopkinson, M. N.; Wencel-Delord J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236-10254.
4. For selected examples of palladium-catalysed direct arylations of heteroaromatics: a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951-1958; b) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074-5075; c) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379-1382; d) Cerna, I.; Pohl, R.; Klepetarova, B.; Hocek, M. *Org. Lett.* **2006**, *8*, 5389-5392; e) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996-8000; f) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476-1479; g) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276-3277; h) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851-1854; i) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622-14623; j) Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749-759; k) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471-483; l) Dröge, T.; Notzon, A.; Fröhlich, R.; Glorius, F. *Chem. Eur. J.* **2011**, *17*, 11974-11977.
5. For selected examples palladium-catalysed direct arylations of heteroarenes from our laboratory: a) Derridj, F.; Roger, J.; Djebbar, S.; Doucet, H. *Org. Lett.* **2010**, *12*, 4320-4323; b) Beydoun, K.; Doucet, H. *ChemSusChem* **2011**, *4*, 526-534; c) Beydoun, K.; Zaarour, M.; Williams, J. A. G.;

Doucet, H.; Guerchais, V. *Chem. Commun.* **2012**, *48*, 1260-1262; d) Bensaid, S.; Doucet, H. *ChemSusChem* **2012**, *5*, 1559-1567; e) Fu, H. Y.; Zhao, L.; Bruneau, C.; Doucet, H. *Synlett* **2012**, 2077-2082.

6. For examples of palladium-catalysed direct heteroarylations of vinyl halide derivatives: a) Gottumukkala, A. L.; Derridj, F.; Djebbar S.; Doucet, H. *Tetrahedron Lett.* **2008**, *49*, 2926-2930; b) Verrier, C.; Hoarau C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647-650; c) Besselievre, F.; Lebrequier, S.; Mahuteau-Betzer F.; Pigel, S. *Synthesis* **2009**, 3511-3518; d) Sahnoun, S.; Messaoudi, S.; Brion J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6097-6102; e) Vabre, R.; Chevot, F.; Legraverend, M.; Pigel, S. *J. Org. Chem.* **2011**, *76*, 9542-9547; f) Beydoun, K.; Roger, J.; Boixel, J.; Le Bozec, H.; Guerchais, V.; Doucet, H. *Chem. Commun.* **2012**, *48*, 11951-11953.
7. For direct arylations of 4-chromanones: a) Bellina, F.; Masini, T.; Rossi, R. *Eur. J. Org. Chem.* **2010**, 1339-1344; b) Lessi, M.; Masini, T.; Nucara, L.; Bellina, F.; Rossi, R. *Adv. Synth. Catal.* **2011**, *353*, 501-507.
8. For a review on the synthesis of asymmetric chromanones: Nibbs, A. E.; Scheidt, K. A. *Eur. J. Org. Chem.* **2012**, 449-462.
9. For "Concerted metallation deprotonation" mechanism: a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754-13755; b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118-1126.
10. Théveau, L.; Verrier, C.; Lassalas, P.; Martin, T.; Dupas, G.; Querolle, O.; Van Hijfte, L.; Marsais, F.; Hoarau, C. *Chem. Eur. J.* **2011**, *17*, 14450-14463.
11. Typical experiment for the synthesis of products **1**-**21**: The reaction of the 3-bromochromen-4-one (0.225 g, 1 mmol), heteroarene (2 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C during 16 h in DMAc (4 mL) with $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol), under argon affords the coupling product after evaporation of the solvent and purification on silica gel. **3-(2-Ethyl-4-methylthiazol-5-yl)-chromen-4-one (1)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 2.96 (q, *J* = 7.6 Hz, 2H), 2.38 (s, 1H), 1.34 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 172.6, 156.1, 154.3, 149.7, 134.0, 126.4, 125.6, 123.8, 119.3, 118.1, 117.9, 26.9, 16.4, 14.2. elemental analysis: calcd (%) for $C_{15}H_{13}NO_2S$ (271.34): C 66.40, H 4.83; found: C 66.25, H 4.98.